PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 13 March 2001 (13.03.01)	
International application No. PCT/CA00/00789	**Applicant's or agent's file reference** N1640013
International filing date (day/month/year) 05 July 2000 (05.07.00)	**Priority date** (day/month/year) 06 July 1999 (06.07.99)
Applicant HOFFER, Joaquin, Andres	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

05 February 2001 (05.02.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Claudio Borton
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
N1640013		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 00/00789	05/07/2000	06/07/1999
Applicant		
NEUROSTREAM TECHNOLOGIES, INC. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   ELECTRICAL STIMULATION SYSTEM FOR TREATING PHANTOM LIMB PAIN

5. With regard to the **abstract,**

   [ ] the text is approved as submitted by the applicant

   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [X] as suggested by the applicant.

   [ ] None of the figures

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 00/00789

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11, 18
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-10, 19

Electrical stimulation system for treating phantom limb pain in an amputee having a limb stump, comprising :
a) a plurality of electrodes implanted in said limb stump,
b) an electrical signal generator for providing each electrode with varying signals.

2. Claims: 12-17

A system for providing sensory feedback from a prosthetic limb to an amputee having a limb stump, comprising :
a) a prosthetic limb having a plurality of sensors for sensing states of touch, or pressure, or force, or slip, or joint position or temperature,
b) a signal transducer for transducing the sensor signals
c) a multi-chambered nerve cuff implanted in said limb stump,
d) means for communicating the electrical signals to a predetermined electrode in said nerve cuff.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 00/00789

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

This invention relates to a system and methods for relieving phantomlimb pain in amputees, and for providing an amputee with sensory feedback from a prosthetic limb (40). The system employs implantable multichannel, multi-chambered interface structures, namely, nerve cuffs (30) The implanted nerve cuffs have electrodes (14) which transmit electrical signals generated by a signal generator (12) to nerves (20), recruiting certain neurons to send sensory signals to the cerebral cortex, suggesting sensory sensations to the amputee. Such signals can arise directly from the signal generator, approximating the train of signals seen by the cortex in a normally innervated limb, or can originate from sensors (50a-c) in a prosthetic limb.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 00/00789

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61N1/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61N A61F A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 232 679 A (SCHULMAN JOSEPH H) 11 November 1980 (1980-11-11) column 1, line 11 -column 3, line 28 column 4, line 26 - line 49; figures	1,19
A	US 5 824 027 A (CHEN YUNQUAN ET AL) 20 October 1998 (1998-10-20) cited in the application column 5, line 60 -column 7, line 53; figures	1,2,12, 19
A	US 5 851 223 A (LITVINOV GRIGORIY S ET AL) 22 December 1998 (1998-12-22) column 3, line 41 -column 4, line 56 column 10, line 47 -column 11, line 12; figures	1,19

-/--

[X] Further documents are listed in the continuation of box C

[X] Patent family members are listed in annex

° Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 February 2001	27. 02. 01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Rakotondrajaona, C

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 25552 A (SCHWABE G BLAINE IV ;SABOLICH JOHN A (US); NOVACARE ORTHOTICS AND) 18 June 1998 (1998-06-18) page 5, line 33 -page 8, line 30 page 24, line 28 -page 25, line 38; figures	12,13, 15,16
A	US 5 413 611 A (HASLAM II THOMAS P ET AL) 9 May 1995 (1995-05-09) column 2, line 61 -column 4, line 14; figures	12,13, 15,16
A	DE 44 04 842 A (FOSS PIERRE NICOLAS DR MED) 17 August 1995 (1995-08-17) abstract	1,19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 00/00789

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4232679 A	11-11-1980	DE 2803366 A	27-07-1978
		FR 2379104 A	25-08-1978
US 5824027 A	20-10-1998	AU 8846798 A	08-03-1999
		WO 9908746 A	25-02-1999
		EP 1001827 A	24-05-2000
US 5851223 A	22-12-1998	US 5571149 A	05-11-1996
		US 5109847 A	05-05-1992
		US 5421817 A	06-06-1995
WO 9825552 A	18-06-1998	AU 5372398 A	03-07-1998
		EP 0964661 A	22-12-1999
US 5413611 A	09-05-1995	NONE	
DE 4404842 A	17-08-1995	NONE	

PATENT COOPERATION TREATY

N164-

RECEIVED
SEP 27 2001
OYEN WIGGS GREEN & MUTALA
PCT

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

KONDOR, George F.
OYEN WIGGS GREEN & MUTALA
480 - 601 West Cordova Street
Vancouver, B.C. V6B 1G1
CANADA

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	21.09.2001
Applicant's or agent's file reference ./.	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00789	05/07/2000	06/07/1999

Applicant
NEUROSTREAM TECHNOLOGIES, INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx 523656 epmu d Fax: +49 89 2399 - 4465	Edel, M Tel. +49 89 2399-2426

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
./.		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00789	05/07/2000	06/07/1999
International Patent Classification (IPC) or national classification and IPC A61N1/34		
Applicant NEUROSTREAM TECHNOLOGIES, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05/02/2001	21.09.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer KÖRBER, C. Telephone No. +49 89 2399 2278

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00789

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1,7-19	as originally filed	
2-6,6a,20	with telefax of	17/08/2001

Claims, No.:

1-13,19 (part)	as originally filed	
14-18,19 (part)	with telefax of	17/08/2001

Drawings, sheets:

1/3-3/3	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 11,18.

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 11,18.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.
   ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00789

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 7-10,12-17
	No:	Claims 1-6,19
Inventive step (IS)	Yes:	Claims 8-10,12-17
	No:	Claims 1-7,19
Industrial applicability (IA)	Yes:	Claims 1-10,12-17,19
	No:	Claims

2. Citations and explanations
   see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item IV

Lack of unity of invention

The application lacks unity (Rule 13.1 PCT) as explained in the "Invitation to pay additional fees" dated 6/11/00, the separate groups of inventions being

1. claims 1-10 and 19;
2. claims 12-17.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents cited in the ISR:

D1: US-A-4 232 679
D2: US-A-5 824 027
D3: WO-A-9 825 552.

1st claimed invention:

1.1 The features of claim 1 (reformulated as suggested under Item VIII below) are known from D1 (see reference numerals 14, 15a, 15b and col. 1, l. 33).

1.2 The subject-matter of claim 1 is also anticipated by document D2 (col. 7, l. 54-65).

1.3 The structural features of independent claim 19 correspond to those of claim 1 and are therefore also known from D1 and D2.

1.4 Accordingly the subject-matter of independent claims 1 and 19 is not new (Article 33(2) PCT).

2. Dependent claims 2-7 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in

respect of novelty and/or inventive step (Article 33(2) and (3) PCT), the reasons being as follows:

2.1 The features of claims 2-6 are also known from D2 (see Fig. 1 and col. 7, l. 54-65).

2.2 Nothing inventive can be recognized in the signal generator being contained within a prosthetic limb as defined in claim 7.

3. The subject-matter of claim 8 is not disclosed or fairly suggested in the available prior art. It is thereby possibile to provide a stream of sigals to the nerve which approximates the normal stream. Accordingly, claim 8, and claims 9 & 10 which are dependent thereon, would appear to meet the requirements of Article 33(2)-(4) PCT (if clarified as indicated under Item VIII).

2nd claimed invention:

4. Document D3 as closest prior art discloses a system comprising features a) and b) of claim 12. The problem to be solved by the present invention is to a achieve a more selective stimulation of the nerve fibers. The solution resides in the provision of a multi-chambered nerve cuff and means for communicating as defined in features c) and d) of claim 12. Although multi-chambered nerve cuffs of this kind are known per se, for instance from D2 as acknowledged on p. 13 of the description of the present application, there is no hint towards their incorporation into a feedback system. D3 gives no suggestion to deviate from the vibratory feedback system disclosed therein. Accordingly, claim 12 and dependent claims 13-17 (if clarified as indicated under Item VIII), which relate to preferred embodiments of the invention, meet the requirements of Article 33(2)-(4) PCT.

Re Item VII

Certain defects in the international application

1. The independent claims are not in the two-part form in accordance with Rule

6.3(b) PCT, which in the present case would be appropriate, with those features known in combination from the prior art (see item V) being placed in a preamble (Rule 6.3(b)(i) PCT) and with the remaining features being included in a characterising part (Rule 6.3(b)(ii) PCT).

2. The features of the claims are not provided with reference signs placed in parentheses (Rule 6.2(b) PCT).

3. The description is not in conformity with the claims as required by Rule 5.1(a)(iii) PCT.

4. The passage from p. 9, l. 20 to p. 10, l. 8 appears to be repetitious.

5. The incorporation of documents by reference (p. 13, 2nd para) is not allowable in some of the Designated States.

Re Item VIII

Certain observations on the international application

1. Claim 1 is not clear (Article 6 PCT) in that it defines that the electrodes are implanted in the limp stump and placed in close proximity to a nerve. This seems to imply that parts of the body of the amputee also form part of the claimed subject-matter. This objection could have been overcome by reformulating the claim in terms of the electrodes being adapted to be implanted, etc. Analogous objections apply to claims 12 and 19.

2. Apparatus claims 5, 6, 10, 15, and 16 relate to methods of using the apparatus rather than clearly defining the apparatus in terms of its technical features. The intended limitations are therefore not clear from these claims, contrary to the requirements of Article 6 PCT.

3. Although claims 1 and 19 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is

sought and in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness. Moreover, lack of clarity of the claims as a whole arises, since the plurality of independent claims makes it difficult, if not impossible, to determine the matter for which protection is sought, and places an undue burden on others seeking to establish the extent of the protection. Hence, claims 1 and 19 do not meet the requirements of Article 6 PCT.

In order to overcome this objection, it would have been appropriate to file an amended set of claims defining the relevant subject-matter in terms of a single independent claim in each category (for each claimed invention as indicated under Item IV) followed by dependent claims covering features which are merely optional (Rule 6.4 PCT).

4. The vague and imprecise statement in the description on p. 19, l. 23-26 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them (see also the PCT Guidelines, III-4.3a).

10/030973
JC13 Rec'd PCT/PTO 0 4 JAN 2002

regions of the cerebral cortex and in particular in the primary sensory cortex associated with the amputated limb can greatly increase their receptivity to synaptic inputs arising from the sensory nerves that remain in the limb stump but are now disconnected from their sensory end-organs.

Cortical neurons can also become more receptive to sensory input arising from other regions of the body, in particular from regions that normally project to areas of cortex adjacent to the cortical areas originally dedicated to the amputated limb or body parts. This cortical response process, described as "cortical plasticity" (Ramachandran, V.S., and Hirstein, W. (1998). *The Perception of Phantom Limbs.* The D.O. Hebb lecture. Brain 121: 1603-1630), can manifest itself as early as 2 hours after experimental digit nerve amputation in animal models (Merzenich MM, Kaas JH, Wall JT, Sur M, Nelson RJ, Felleman DJ. (1983) *Progession of Change Following Median Nerve Section in the Cortical Representation of the Hand in Areas 3b and 1 in Adult Owl and Squirrel Monkeys.* Neuroscience 10(3):639-65); (Kaas JH. (1998) *Phantoms of the Brain.* Nature 391(6665):331, 333) and continues to develop for many weeks and months if peripheral nerves remain transected and cannot reestablish contact with their original or other suitable target organs.

It is believed that this greatly increased responsiveness of cortical neurons to inappropriate sensory inputs is at least partly responsible for phantom limb sensations. Phantom limb sensations are thus interpreted to arise from the missing limb or digits, even though the sensations may be triggered by sensory receptors from other body regions or by random activity in the disconnected sensory endings within the amputated limb stump.

Such phantom limb sensations may or may not include pain components. When pain is present, it is sometimes of such intensity that it becomes unbearable or extremely disabling to the amputee. One possibility which may account for the occurrence of phantom limb pain is that amputation eliminates or greatly disrupts the normal flow of sensory information arising from other modalities of sensory receptors (e.g., low-threshold cutaneous or muscle receptors) carried by larger diameter, myelinated axons. These sensory axons normally convey non-painful information of proprioceptive and cutaneous origin such as touch, pressure, temperature, muscle length, tendon force or joint position.

An important landmark in the pain scientific literature is the work by Wall and Melzack ((1965) *Pain Mechanisms: A New Theory*. Science 150(699):971-9), who in the 1960's proposed the "Gate Control Theory" of pain whereby activity in large diameter touch Ab nerve fibers were hypothesized to reduce the central transmission of pain activity information carried to the spinal cord by smaller Aδ and C fibers. Although this hypothesis remains controversial, it has brought a focus on the complex interactions that can exist among parallel sensory inputs of different modalities, and on the various central and peripheral factors that can contribute to the central perception of pain. It is now generally accepted that the balance of activity in large and small diameter sensory nerve fibers is important in pain transmission in the spinal cord and brain centers.

In one theory of synaptic connectivity in the central nervous system, proposed by Wall and Melzack, synaptic input from large myelinated sensory fibers normally converge on interneurons that mediate pain

pathway information and tend to inhibit the transmission of pain sensations that are conducted by smaller diameter, unmyelinated sensory nerve fibers. In the absence of proprioceptive and cutaneous information that could inhibit the transmission of pain, the pain pathways are open. The sensations of pain that reach the cortex are interpreted to arise from the missing limb or digits (thus the term "phantom limb" pain), even though the sensations may be triggered by sensory receptors from other body regions, or by random activity in pain afferents in the nerve stumps in the amputated limb or digits.

With respect to the fate of nerve fibers in amputated limbs, it is known that all nerve fibers in a severed nerve may atrophy to some extent in the sense that the fiber diameters are reduced, but the nerve cells generally remain viable in the sense that they continue to conduct electrical impulses and retain their basic synaptic connectivity patterns. It is also known that sensory fibers atrophy relatively more than motor fibers (Hoffer, J.A., Stein, R.B. and Gordon, T. (1979) *Differential Atrophy of Sensory and Motor Fibers Following Section of Cat Peripheral Nerves.* Brain Res. 178:347-361) and, furthermore, that large-diameter sensory fibers typically atrophy more than small-diameter sensory fibers. Similarly, large-diameter motor fibers typically atrophy more than small-diameter motor fibers. For hind limb nerves of cats that were cut and ligated over a period of 300 days, Milner et al. ((1981) *The Effects of Axotomy on the Condition of Action Potentials in Peripheral Sensory and Motor Nerve Fibres.* J Neurol Neurosurg Psychiatry 44(6):485-96) found that large sensory fibers had a 60% decrease in conduction velocity (CV); small sensory fibers had about a 45% decrease in CV; large motor fibers had a 40% decrease in CV; and small motor fibers had about a 20% decrease in

CV. Thus, in amputated nerves, "large" and "small" nerve fibers will gradually become closer in their diameters and consequently closer in their thresholds for electrical stimulation.

Description of Prior Art

Various pharmacological approaches have been proposed for treating phantom limb pain. Analgesics have generally not worked against this kind of pain. Antidepressant medications can reduce the sensation of pain, but have serious side effects that have limited their applicability. There are currently no approved drugs that are recognized to treat phantom limb pain safely and effectively without unwanted side effects. Another approach, the blockade or removal of the sympathetic supply to the stump, can provide temporary reduction of phantom pain but the effects depend on how soon after amputation the procedure is done, and may not be long-lasting (Livingston KE (1945) *Phantom Limb Syndrome. A Discussion of the Role of Major Peripheral Nerve Neuromas.* J. Neurosurgery 2:251-5).

It is known that electrical stimulation of nervous structures can be effective in providing relief of certain types of peripheral pain. Two main approaches used to date are transcutaneous electrical nerve stimulation (TENS) and dorsal column stimulation (DCS) in the spinal cord. It is likely that the mode of action of these therapies involves the stimulation of large diameter sensory fibers in limb nerves (TENS) or in the spinal cord (DCS), reducing the transmission of pain in central pathways described by the Gate Control Theory.

However, application of these electrical stimulation techniques has had only modest success for treatment of phantom limb pain in amputees. It is likely that TENS ceases to be effective as the sensory fibers in amputated nerves become gradually thinner. As they do so, their electrical thresholds gradually rise, to the point that the fibers can no longer be recruited effectively with TENS.

There is some limited evidence that it is possible to selectively stimulate large-diameter sensory fibers in severed nerves of amputees by providing electrical stimulation, thereby eliciting touch sensations without causing any concomitant pain sensations. Stein, R.B., Charles, D., Hoffer, J.A., Arsenault, J., Davis, L.A., Moorman, S. and Moss, B. (1980) *New Approaches to Controlling Powered Arm Prostheses, Particularly by High-Level Amputees.* Bull. Prosth. Res. 17:51-62, showed that it is possible to elicit sensations that the amputee interpreted to arise from an amputated limb, by electrically stimulating sensory axons in a ligated peripheral nerve inside the forearm stump of a below-elbow arm amputee. Even though the arm had been amputated over 30 years earlier, the amputee subject was able to clearly sense the stimulation, which he reported as a non-noxious tingling sensation arising from the ulnar aspect of his phantom limb, specifically from the ring and small fingers which is the sensory field that is normally innervated by the ulnar nerve. The amputee was able to subjectively discriminate frequencies of stimulation ranging from single pulses to steady rates up to 10-20 Hz. For frequencies greater than 20 Hz the sensations were reported as either fused or absent, indicating that the nerve fibers could have been fatigued by high-frequency stimulation in this patient. This reference suggests that severed sensory nerve fibers in

amputees can survive for 30 years or longer in the absence of suitable connections to sensory end-organs.

Sculman (U.S. Patent No. 4,232,679) and Schwabe (WO 98/25552) describe systems for providing stimuli to human tissues, but do not have the advantages provided by the present invention.

signals produced by a signal generator be transmitted to nerve 20 electrically. The nerve cuff 30 may support the mechanical anchoring of one or more signal transducers, their associated conductors and associated signal processing units. For example, it may be appropriate to have an electrochemical, pharmacological and/or optical system to transduce signals from the signal generator 12 to recruit neurons in nerve 30. Such a pharmacological system 70, which includes catheters 25, is also shown in Figure 1.

Further, while the system described herein is described with particular application to amputees, it may also suitably be employed with appropriate modification to work in subjects with other peripheral nerve injuries other than those caused by amputation.

Accordingly, the scope of the invention is to be construed in accordance with the substance defined by the following claims.

14. The system as claimed in claim 13 wherein said non-electrically signal transmission comprises telemetric transmission across the skin of the amputee.

15. The system as claimed in claim 14 wherein a plurality of unique electrical signals are communicated to said electrodes, providing stimulation to said nerve approximating the pattern of stimulation arising from an unamputated, normally innervated limb.

16. The system as claimed in claim 15 wherein said predetermined electrode, when sent its signal, stimulates that portion of said nerve which provides to the amputee an appropriate sensation.

17. The system as claimed in claim 12 comprising a plurality of nerve cuffs, each one surrounding a different nerve.

18. A method for providing an amputee with sensory feedback from a prosthetic limb, comprising the steps of:

a) equipping an amputee with the system claimed in any one of claims 12-17; and

b) providing sensory stimuli to said prosthetic limb.

19. A system for alleviating pain in a person having a peripheral nerve injury, said system comprising:

a) a plurality of electrodes implanted in said person, said electrodes placed in close proximity to an injured sensory nerve in said person,

regions of the cerebral cortex and in particular in the primary sensory cortex associated with the amputated limb can greatly increase their receptivity to synaptic inputs arising from the sensory nerves that remain in the limb stump but are now disconnected from their sensory end-organs.

Cortical neurons can also become more receptive to sensory input arising from other regions of the body, in particular from regions that normally project to areas of cortex adjacent to the cortical areas originally dedicated to the amputated limb or body parts. This cortical response process, described as "cortical plasticity" (Srindvasan et al, 1991), can manifest itself as early as 2 hours after experimental digit nerve amputation in animal models (Merzenich et al., 1983; Kaas, 1998) and continues to develop for many weeks and months if peripheral nerves remain transected and cannot reestablish contact with their original or other suitable target organs.

It is believed that this greatly increased responsiveness of cortical neurons to inappropriate sensory inputs is at least partly responsible for phantom limb sensations. Phantom limb sensations are thus interpreted to arise from the missing limb or digits, even though the sensations may be triggered by sensory receptors from other body regions or by random activity in the disconnected sensory endings within the amputated limb stump.

Such phantom limb sensations may or may not include pain components. When pain is present, it is sometimes of such intensity that

it becomes unbearable or extremely disabling to the amputee. One possibility which may account for the occurrence of phantom limb pain is that amputation eliminates or greatly disrupts the normal flow of sensory information arising from other modalities of sensory receptors (e.g., low-threshold cutaneous or muscle receptors) carried by larger diameter, myelinated axons. These sensory axons normally convey non-painful information of proprioceptive and cutaneous origin such as touch, pressure, temperature, muscle length, tendon force or joint position.

An important landmark in the pain scientific literature is the work by Wall and Melzack, who in the 1960's proposed the "Gate Control Theory" of pain whereby activity in large diameter touch Ab nerve fibers were hypothesized to reduce the central transmission of pain activity information carried to the spinal cord by smaller Aδ and C fibers. Although this hypothesis remains controversial, it has brought a focus on the complex interactions that can exist among parallel sensory inputs of different modalities, and on the various central and peripheral factors that can contribute to the central perception of pain. It is now generally accepted that the balance of activity in large and small diameter sensory nerve fibers is important in pain transmission in the spinal cord and brain centers.

In one theory of synaptic connectivity in the central nervous system, proposed by Wall and Melzack, synaptic input from large myelinated sensory fibers normally converge on interneurons that mediate pain pathway information and tend to inhibit the transmission of pain sensations

that are conducted by smaller diameter, unmyelinated sensory nerve fibers. In the absence of proprioceptive and cutaneous information that could inhibit the transmission of pain, the pain pathways are open. The sensations of pain that reach the cortex are interpreted to arise from the missing limb or digits (thus the term "phantom limb" pain), even though the sensations may be triggered by sensory receptors from other body regions, or by random activity in pain afferents in the nerve stumps in the amputated limb or digits.

With respect to the fate of nerve fibers in amputated limbs, it is known that all nerve fibers in a severed nerve may atrophy to some extent in the sense that the fiber diameters are reduced, but the nerve cells generally remain viable in the sense that they continue to conduct electrical impulses and retain their basic synaptic connectivity patterns. It is also known that sensory fibers atrophy relatively more than motor fibers (Hoffer et al., 1979) and, furthermore, that large-diameter sensory fibers typically atrophy more than small-diameter sensory fibers. Similarly, large-diameter motor fibers typically atrophy more than small-diameter motor fibers. For hind limb nerves of cats that were cut and ligated over a period of 300 days, Milner et al. (1981) found that large sensory fibers had a 60% decrease in conduction velocity (CV); small sensory fibers had about a 45% decrease in CV; large motor fibers had a 40% decrease in CV; and small motor fibers had about a 20% decrease in CV. Thus, in amputated nerves, "large" and "small" nerve fibers will gradually become closer in their diameters and consequently closer in their thresholds for electrical stimulation.

Description of Prior Art

Various pharmacological approaches have been proposed for treating phantom limb pain. Analgesics have generally not worked against this kind of pain. Antidepressant medications can reduce the sensation of pain, but have serious side effects that have limited their applicability. There are currently no approved drugs that are recognized to treat phantom limb pain safely and effectively without unwanted side effects. Another approach, the blockade or removal of the sympathetic supply to the stump, can provide temporary reduction of phantom pain but the effects depend on how soon after amputation the procedure is done, and may not be long-lasting (Livingston, 1945).

It is known that electrical stimulation of nervous structures can be effective in providing relief of certain types of peripheral pain. Two main approaches used to date are transcutaneous electrical nerve stimulation (TENS) and dorsal column stimulation (DCS) in the spinal cord. It is likely that the mode of action of these therapies involves the stimulation of large diameter sensory fibers in limb nerves (TENS) or in the spinal cord (DCS), reducing the transmission of pain in central pathways described by the Gate Control Theory.

However, application of these electrical stimulation techniques has had only modest success for treatment of phantom limb pain in amputees. It is likely that TENS ceases to be effective as the sensory fibers in amputated nerves become gradually thinner. As they do so, their

electrical thresholds gradually rise, to the point that the fibers can no longer be recruited effectively with TENS.

There is some limited evidence that it is possible to selectively stimulate large-diameter sensory fibers in severed nerves of amputees by providing electrical stimulation, thereby eliciting touch sensations without causing any concomitant pain sensations. Stein et al. (1980) showed that it is possible to elicit sensations that the amputee interpreted to arise from an amputated limb, by electrically stimulating sensory axons in a ligated peripheral nerve inside the forearm stump of a below-elbow arm amputee. Even though the arm had been amputated over 30 years earlier, the amputee subject was able to clearly sense the stimulation, which he reported as a non-noxious tingling sensation arising from the ulnar aspect of his phantom limb, specifically from the ring and small fingers which is the sensory field that is normally innervated by the ulnar nerve. The amputee was able to subjectively discriminate frequencies of stimulation ranging from single pulses to steady rates up to 10-20 Hz. For frequencies greater than 20 Hz the sensations were reported as either fused or absent, indicating that the nerve fibers could have been fatigued by high-frequency stimulation in this patient. This reference suggests that severed sensory nerve fibers in amputees can survive for 30 years or longer in the absence of suitable connections to sensory end-organs.

signals produced by a signal generator be transmitted to nerve 20 electrically. The nerve cuff 30 may support the mechanical anchoring of one or more signal transducers, their associated conductors and associated signal processing units. For example, it may be appropriate to have an electrochemical, pharmacological and/or optical system to transduce signals from the signal generator 12 to recruit neurons in nerve 30. Such a pharmacological system 60 is also shown in Figure 1.

Further, while the system described herein is described with particular application to amputees, it may also suitably be employed with appropriate modification to work in subjects with other peripheral nerve injuries other than those caused by amputation.

Accordingly, the scope of the invention is to be construed in accordance with the substance defined by the following claims.

14. The system as claimed in claim 13 wherein said non-electrically signal transmission comprises telemetric transmission across the skin of the amputee.

15. The system as claimed in claim 14 wherein a plurality of unique electrical signals are communicated to said electrodes, providing stimulation to said nerve approximating the pattern of stimulation arising from an unamputated, normally innervated limb.

16. The system as claimed in claim 15 wherein said predetermined electrode, when sent its signal, stimulates that portion of said nerve which provides to the amputee an appropriate sensation.

17. The system as claimed in claim 10 comprising a plurality of nerve cuffs, each one surrounding a different nerve.

18. A method for providing an amputee with sensory feedback from a prosthetic limb, comprising the steps of:

a) equipping an amputee with the system claimed in any one of claims 12-17; and

b) providing sensory stimuli to said prosthetic limb.

19. A system for alleviating pain in a person having a peripheral nerve injury, said system comprising:

a) a plurality of electrodes implanted in said person, said electrodes placed in close proximity to an injured sensory nerve in said person,

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(75) Inventor/Applicant *(for US only)*: HOFFER, Joaquin, Andres [CA/CA]; 241 Strong Road, Anmore, British Columbia V3H 3C8 (CA).

(74) Agent: KONDOR, George, F.; Oyen Wiggs Green & Mutala, 480 - 601 West Cordova Street, Vancouver, British Columbia V6B 1G1 (CA).

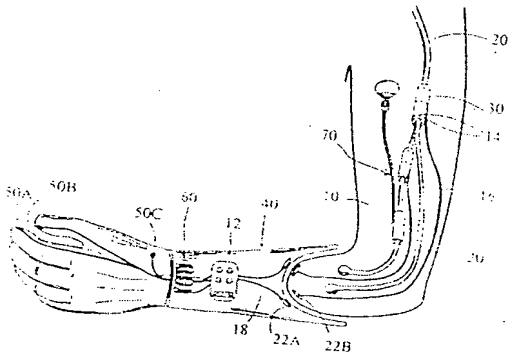
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ELECTRICAL STIMULATION SYSTEM AND METHODS FOR TREATING PHANTOM LIMB PAIN AND FOR PROVIDING SENSORY FEEDBACK TO AN AMPUTEE FROM A PROSTHETIC LIMB



(57) Abstract: This invention relates to a system and methods for relieving phantom limb pain in amputees and for providing an amputee with sensory feedback from a prosthetic limb. The system employs implantable multi-channel, multi-functional interface structures, namely, nerve cuffs. The implanted nerve cuffs have electrodes which transmit electrical signals generated by a signal generator to nerves, recruiting certain neurons to send sensory signals to the cerebral cortex, suggesting sensory sensations to the amputee. Such signals can arise directly from the signal generator, approximating the train of signals seen by the cortex in a normally innervated limb, or can originate from sensors in a prosthetic limb.

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(71) Applicant *(for all designated States except US)*: NEUROSTREAM TECHNOLOGIES, INC. [CA/CA]; 241 Strong Road, Anmore, British Columbia V3H 3C8 (CA).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: HOFFER, Joaquin, Andres [CA/CA]; 241 Strong Road, Anmore, British Columbia V3H 3C8 (CA).

(74) Agent: KONDOR, George, F.; Oyen Wiggs Green & Mutala, 480 - 601 West Cordova Street, Vancouver, British Columbia V6B 1G1 (CA).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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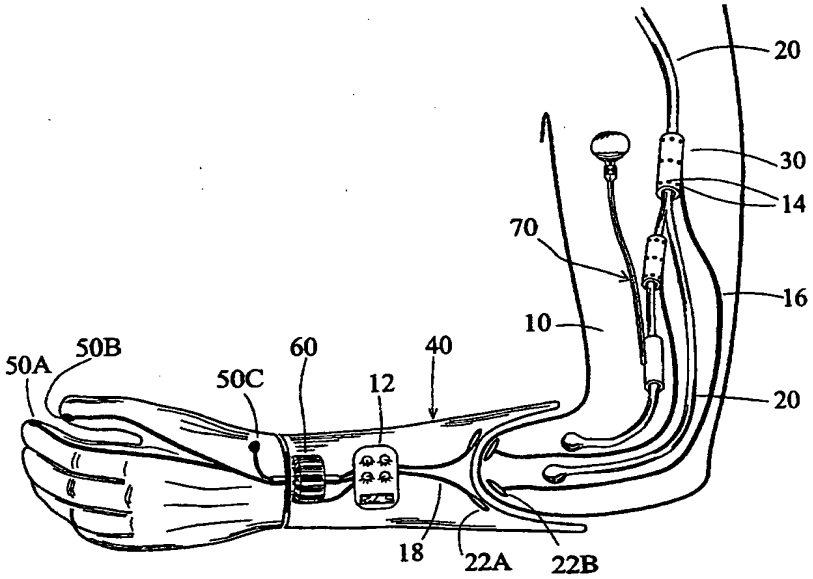
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ELECTRICAL STIMULATION SYSTEM FOR TREATING PHANTOM LIMB PAIN



(57) Abstract: This invention relates to a system and methods for relieving phantomlimb pain in amputees, and for providing an amputee with sensory feedback from a prosthetic limb (40). The system employs implantable multichannel, multi-chambered interface structures, namely, nerve cuffs (30). The implanted nerve cuffs have electrodes (14) which transmit electrical signals generated by a signal generator (12) to nerves (20), recruiting certain neurons to send sensory signals to the cerebral cortex, suggesting sensory sensations to the amputee. Such signals can arise directly from the signal generator, approximating the train of signals seen by the cortex in a normally innervated limb, or can originate from sensors (50a-c) in a prosthetic limb.

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INTERNATIONAL SEARCH REPORT

In. ational Application No
PCT/CA 00/00789

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61N1/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61N A61F A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 232 679 A (SCHULMAN JOSEPH H) 11 November 1980 (1980-11-11) column 1, line 11 -column 3, line 28 column 4, line 26 - line 49; figures ---	1,19
A	US 5 824 027 A (CHEN YUNQUAN ET AL) 20 October 1998 (1998-10-20) cited in the application column 5, line 60 -column 7, line 53; figures ---	1,2,12, 19
A	US 5 851 223 A (LITVINOV GRIGORIY S ET AL) 22 December 1998 (1998-12-22) column 3, line 41 -column 4, line 56 column 10, line 47 -column 11, line 12; figures ---	1,19
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 February 2001	27. 02. 01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rakotondrajaona, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 00/00789

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 25552 A (SCHWABE G BLAINE IV ;SABOLICH JOHN A (US); NOVACARE ORTHOTICS AND) 18 June 1998 (1998-06-18) page 5, line 33 -page 8, line 30 page 24, line 28 -page 25, line 38; figures	12,13, 15,16
A	US 5 413 611 A (HASLAM II THOMAS P ET AL) 9 May 1995 (1995-05-09) column 2, line 61 -column 4, line 14; figures	12,13, 15,16
A	DE 44 04 842 A (FOSS PIERRE NICOLAS DR MED) 17 August 1995 (1995-08-17) abstract	1,19

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 00/00789

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11, 18
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-10, 19

   Electrical stimulation system for treating phantom limb pain in an amputee having a limb stump, comprising :
   a) a plurality of electrodes implanted in said limb stump,
   b) an electrical signal generator for providing each electrode with varying signals.

2. Claims: 12-17

   A system for providing sensory feedback from a prosthetic limb to an amputee having a limb stump, comprising :
   a) a prosthetic limb having a plurality of sensors for sensing states of touch, or pressure, or force, or slip, or joint position or temperature,
   b) a signal transducer for transducing the sensor signals
   c) a multi-chambered nerve cuff implanted in said limb stump,
   d) means for communicating the electrical signals to a predetermined electrode in said nerve cuff.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 00/00789

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4232679 A	11-11-1980	DE 2803366 A	27-07-1978
		FR 2379104 A	25-08-1978
US 5824027 A	20-10-1998	AU 8846798 A	08-03-1999
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		EP 0964661 A	22-12-1999
US 5413611 A	09-05-1995	NONE	
DE 4404842 A	17-08-1995	NONE	

ELECTRICAL STIMULATION SYSTEM AND METHODS FOR TREATING PHANTOM LIMB PAIN AND FOR PROVIDING SENSORY FEEDBACK TO AN AMPUTEE FROM A PROSTHETIC LIMB

Technical Field

This invention relates to a system and methods for electrical stimulation of body tissues, and more particularly to a system and methods for stimulating nerves to alleviate phantom limb pain in an amputee, and/or for providing sensory feedback from a prosthetic limb worn by an amputee.

Background

Limb amputations cause three major types of dysfunction. Two of these occur immediately, and are direct consequences of the amputation: the loss of motor function below the amputation level; and the loss of all sensory feedback arising from the missing limb below the amputation level.

The third, more indirect dysfunctional consequence of amputation is that which is known as "phantom limb" sensations. These may occur either soon after, or at various delayed times after amputation. An amputee having such sensations may still "feel" his or her amputated limb in place. Of particular concern is phantom limb pain, where the amputee feels sensations of pain seemingly arising from the original limb.

The causes for the often very vivid and disturbing phantom limb sensations reported by a majority of limb amputees are not completely understood, but it is believed that several processes are responsible. Subsequent to loss of normal peripheral sensory nerve input, neurons in

regions of the cerebral cortex and in particular in the primary sensory cortex associated with the amputated limb can greatly increase their receptivity to synaptic inputs arising from the sensory nerves that remain in the limb stump but are now disconnected from their sensory end-organs.

Cortical neurons can also become more receptive to sensory input arising from other regions of the body, in particular from regions that normally project to areas of cortex adjacent to the cortical areas originally dedicated to the amputated limb or body parts. This cortical response process, described as "cortical plasticity" (Srindvasan et al, 1991), can manifest itself as early as 2 hours after experimental digit nerve amputation in animal models (Merzenich et al., 1983; Kaas, 1998) and continues to develop for many weeks and months if peripheral nerves remain transected and cannot reestablish contact with their original or other suitable target organs.

It is believed that this greatly increased responsiveness of cortical neurons to inappropriate sensory inputs is at least partly responsible for phantom limb sensations. Phantom limb sensations are thus interpreted to arise from the missing limb or digits, even though the sensations may be triggered by sensory receptors from other body regions or by random activity in the disconnected sensory endings within the amputated limb stump.

Such phantom limb sensations may or may not include pain components. When pain is present, it is sometimes of such intensity that

it becomes unbearable or extremely disabling to the amputee. One possibility which may account for the occurrence of phantom limb pain is that amputation eliminates or greatly disrupts the normal flow of sensory information arising from other modalities of sensory receptors (e.g., low-threshold cutaneous or muscle receptors) carried by larger diameter, myelinated axons. These sensory axons normally convey non-painful information of proprioceptive and cutaneous origin such as touch, pressure, temperature, muscle length, tendon force or joint position.

An important landmark in the pain scientific literature is the work by Wall and Melzack, who in the 1960's proposed the "Gate Control Theory" of pain whereby activity in large diameter touch Ab nerve fibers were hypothesized to reduce the central transmission of pain activity information carried to the spinal cord by smaller Aδ and C fibers. Although this hypothesis remains controversial, it has brought a focus on the complex interactions that can exist among parallel sensory inputs of different modalities, and on the various central and peripheral factors that can contribute to the central perception of pain. It is now generally accepted that the balance of activity in large and small diameter sensory nerve fibers is important in pain transmission in the spinal cord and brain centers.

In one theory of synaptic connectivity in the central nervous system, proposed by Wall and Melzack, synaptic input from large myelinated sensory fibers normally converge on interneurons that mediate pain pathway information and tend to inhibit the transmission of pain sensations

that are conducted by smaller diameter, unmyelinated sensory nerve fibers. In the absence of proprioceptive and cutaneous information that could inhibit the transmission of pain, the pain pathways are open. The sensations of pain that reach the cortex are interpreted to arise from the missing limb or digits (thus the term "phantom limb" pain), even though the sensations may be triggered by sensory receptors from other body regions, or by random activity in pain afferents in the nerve stumps in the amputated limb or digits.

With respect to the fate of nerve fibers in amputated limbs, it is known that all nerve fibers in a severed nerve may atrophy to some extent in the sense that the fiber diameters are reduced, but the nerve cells generally remain viable in the sense that they continue to conduct electrical impulses and retain their basic synaptic connectivity patterns. It is also known that sensory fibers atrophy relatively more than motor fibers (Hoffer et al., 1979) and, furthermore, that large-diameter sensory fibers typically atrophy more than small-diameter sensory fibers. Similarly, large-diameter motor fibers typically atrophy more than small-diameter motor fibers. For hind limb nerves of cats that were cut and ligated over a period of 300 days, Milner et al. (1981) found that large sensory fibers had a 60% decrease in conduction velocity (CV); small sensory fibers had about a 45% decrease in CV; large motor fibers had a 40% decrease in CV; and small motor fibers had about a 20% decrease in CV. Thus, in amputated nerves, "large" and "small" nerve fibers will gradually become closer in their diameters and consequently closer in their thresholds for electrical stimulation.

Description of Prior Art

Various pharmacological approaches have been proposed for treating phantom limb pain. Analgesics have generally not worked against this kind of pain. Antidepressant medications can reduce the sensation of pain, but have serious side effects that have limited their applicability. There are currently no approved drugs that are recognized to treat phantom limb pain safely and effectively without unwanted side effects. Another approach, the blockade or removal of the sympathetic supply to the stump, can provide temporary reduction of phantom pain but the effects depend on how soon after amputation the procedure is done, and may not be long-lasting (Livingston, 1945).

It is known that electrical stimulation of nervous structures can be effective in providing relief of certain types of peripheral pain. Two main approaches used to date are transcutaneous electrical nerve stimulation (TENS) and dorsal column stimulation (DCS) in the spinal cord. It is likely that the mode of action of these therapies involves the stimulation of large diameter sensory fibers in limb nerves (TENS) or in the spinal cord (DCS), reducing the transmission of pain in central pathways described by the Gate Control Theory.

However, application of these electrical stimulation techniques has had only modest success for treatment of phantom limb pain in amputees. It is likely that TENS ceases to be effective as the sensory fibers in amputated nerves become gradually thinner. As they do so, their

electrical thresholds gradually rise, to the point that the fibers can no longer be recruited effectively with TENS.

There is some limited evidence that it is possible to selectively stimulate large-diameter sensory fibers in severed nerves of amputees by providing electrical stimulation, thereby eliciting touch sensations without causing any concomitant pain sensations. Stein et al. (1980) showed that it is possible to elicit sensations that the amputee interpreted to arise from an amputated limb, by electrically stimulating sensory axons in a ligated peripheral nerve inside the forearm stump of a below-elbow arm amputee. Even though the arm had been amputated over 30 years earlier, the amputee subject was able to clearly sense the stimulation, which he reported as a non-noxious tingling sensation arising from the ulnar aspect of his phantom limb, specifically from the ring and small fingers which is the sensory field that is normally innervated by the ulnar nerve. The amputee was able to subjectively discriminate frequencies of stimulation ranging from single pulses to steady rates up to 10-20 Hz. For frequencies greater than 20 Hz the sensations were reported as either fused or absent, indicating that the nerve fibers could have been fatigued by high-frequency stimulation in this patient. This reference suggests that severed sensory nerve fibers in amputees can survive for 30 years or longer in the absence of suitable connections to sensory end-organs.

Summary of Invention

This invention provides a system and methods for alleviating phantom limb pain and for replacing lost sensory function from a missing limb.

Activity flowing centrally along larger diameter sensory fibers can help suppress the central perception of pain information carried by smaller diameter fibers and, as a corollary, when there is an absence of activity that would normally occur in large diameter sensory fibers, such as in touch receptor afferents that have been disconnected from their peripheral sensory organs, there is a greater chance for pain sensations to reach consciousness. This condition, when it occurs in amputees, for example, may be reversed by selective electrical stimulation of the larger sensory fibers to so restore sensory traffic in these fibers, thus restoring a more normal balance of activity in large and small diameter fibers which will counterbalance again the excessive flow of pain information in central pathways.

Specifically, the invention provides a system for alleviating phantom limb pain which has an implanted electrode or electrodes located in, around or near the severed peripheral nerve stumps that remain inside the proximal stump of an amputated limb. Appropriately chosen electrical stimulation parameters can accomplish the following desirable purposes:

1) provide sensory feedback about parameters of a prosthetic limb, such as touch, pressure, force, slip, joint position or temperature information; and/or

2) provide an effective method of treatment of phantom limb pain.

More specifically, the invention provides a system for alleviating phantom limb pain in an amputee having a limb stump, the system comprising a plurality of electrodes implanted in the limb stump, the electrodes placed in close proximity to a severed sensory nerve in the amputee's limb stump, the electrodes when supplied with electrical current providing electrical stimulation to said nerve; and an electrical signal generator fashioned to communicate varying electrical signals to each electrode In a preferred embodiment, the electrodes are incorporated within a tubular nerve cuff fashioned to be implanted in the limb stump so as to circumferentially surround a portion of the nerve.

In a further embodiment, nerve cuff is multi-chambered, and each of the electrodes is segregated into one chamber of the nerve cuff, each electrode thereby being placed in close proximity to a different portion of the nerve.

Alternatively, one or more catheters can provide selective delivery of pharmacological agents to the nerve stumps for the treatment of pain.

In one embodiment, the invention has in particular multi-channel interface structures, which may be implanted to permit stimulation of multiple sites or sensory modalities of internal body tissues, such as nerves, together with selective infusion of chemical substances. The interfaces may be provided in the form of nerve cuffs. The interfaces may provide electrical, chemical and/or optical connections to selected bodily tissues.

Preferred embodiments of the invention increase the effectiveness of selective recruitment with electrical stimulation of large sensory nerve fibers in severed nerve stumps in amputated limbs by providing electrodes which are implanted inside the amputated limb, directly on or very close to the nerve stumps. Because nerve fibers of different diameters atrophy differently, the thresholds for electrical stimulation of large and small sensory fibers tend to gradually move closer together. Placing the stimulating electrodes closer to the nerve provides an improved means for selectively stimulating the large fibers even after they have atrophied as a consequence of the nerve amputation.

More specifically, the invention provides a system for alleviating phantom limb pain in an amputee having a limb stump, the system comprising a plurality of electrodes implanted in the limb stump, the electrodes placed in close proximity to a severed sensory nerve in the amputee's limb stump, the electrodes when supplied with electrical current providing electrical stimulation to said nerve; and an electrical signal generator fashioned to communicate varying electrical signals to each

electrode In a preferred embodiment, the electrodes are incorporated within a tubular nerve cuff fashioned to be implanted in the limb stump so as to circumferentially surround a portion of the nerve.

In a further embodiment, nerve cuff is multi-chambered, and each of the electrodes is segregated into one chamber of the nerve cuff, each electrode thereby being placed in close proximity to a different portion of the nerve. Cuff electrodes are considered to be easier to install and more efficient than other types of electrodes for providing the desired stimulation. Multichannel electrodes are also more efficient for selectively recruiting desired sensory nerve modalities with electrical stimulation. Multi-chambered nerve cuffs are the most preferred design for providing multichannel stimulation.

Another aspect of this invention provides methods of application of non-noxious electrical stimulation of larger, lower-threshold myelinated sensory axons in severed nerve stumps, which may serve to disfacilitate or inhibit the transmission of pain sensations in central pathways. These methods of stimulation may also act to arrest or reduce the evolution of synaptic changes that are believed to occur in the sensory cortex after limb amputation that may be responsible for "phantom limb" sensations, and in particular phantom limb pain sensations.

Brief Description of Drawings

In drawings which illustrate one particular embodiment of the invention,

Figure 1 is a schematic view of an amputee's limb stump and a prosthetic limb equipped with a system for alleviating phantom limb pain and for practising the methods of the invention; and,

Figures 2 and 3 are respectively perspective and cross sectional views of a multi-channel nerve-cuff surrounding a ligated severed nerve in an amputee's stump.

Description

As shown in Fig. 1, the present system for alleviating phantom limb pain in an amputee having a limb stump 10 has a plurality of electrodes 14 (shown in greater detail in Figures 2 and 3) implanted in the limb stump 10, in close proximity to a severed afferent or "sensory" nerve 20 in limb stump 10, which nerve 20 had innervated the amputated limb.

Fashioned to communicate electrical signals to electrodes 14 is an electrical stimulation system such as electrical signal generator 12. Signal generator 12 may be implanted in limb stump 10 and connected directly to electrodes 14 by suitable biocompatible cabling (not shown), or, as shown in Figure 1, signal generator 12 may be outside of the amputee's body.

In this instance, signals communicated by signal generator 12 to electrodes 14 are preferably transmitted telemetrically in part, to avoid

having cabling pass through the amputee's skin. As shown in Figure 1, in the preferred embodiment of the invention signals from signal generator 12 may pass through external cable 18 to transmitting antenna 22A, across the skin of the amputee to receiver antenna 22B, and then through cable 16 to electrodes 14.

As discussed above, each electrode 14 is implanted in limb stump 10 in close proximity to nerve 20. As shown in Figures 2 and 3, nerve 20 may comprise a plurality of nerve fascicles 28 and individual nerve axons 29, all encompassed within the perineurium 27.

It has been determined that electrical signals provided by electrodes 14 to nerve 20 will stimulate or recruit certain portions of nerve 20 (ie. certain neurons), to provide nervous signals, in the form of action potentials, therein. In the context of the description herein, "in close proximity to nerve 20" means that electrodes 14 are implanted in close enough spaced relation to nerve 20 to cause signals to be produced in nerve 20 by transmission of the electrical signals produced by signal generator 12. Accordingly, electrodes 14 may be implanted directly in nerve 20, but may also rest directly on the surface of nerve 20, or may be some small distance away from the surface of nerve 20, as long as the transmission, by electrodes 14, of signals produced by signal generator 12 still causes nervous signals in the form of action potentials to be produced in, and conducted along, nerve 20.

In a preferred embodiment of the present invention, the electrodes 14 of the system are incorporated within a nerve cuff 30 fashioned to circumferentially surround the nerve 20 when implanted. Such a nerve cuff 30 is shown in greater detail in Figures 2 and 3.

As described in Kallesøe et al., U.S. patent No. 5,487,756, and Hoffer et al., U.S. patent No. 5,824,027, both of which are incorporated herein by reference, a nerve cuff is typically a tubular structure having an outer wall which can be used to electrically isolate in vivo a tissue of interest, namely a nerve, inside a lumen defined by the cuff wall. Nerve cuffs which are designed to be chronically implanted are made from suitable biocompatible materials such as medical grades of silicone.

Nerve cuff 30 may be of any suitable design but as shown in these figures the preferred nerve cuff is a multichannel (ie. it has more than one electrode), multi-chambered nerve stimulation cuff. In a preferred embodiment the various apertures for electrodes 14 and catheters 25, if provided, may be cut in the cuff wall by a laser. The significance of catheters 25 is discussed below.

Figures 2 and 3 show the preferred nerve cuff of the present invention placed around a severed nerve in an amputated limb. The preferred multichannel nerve cuff 30 has a closure comprising interdigitated tubular members 32 as described in Kallesøe et al. Nerve cuff 30 is closed by running a long member 31 through tubular members 32 when inter-digitated.

As taught in the prior art, a plurality of electrodes 14 are placed within individual chambers 23 within nerve cuff 30. Chambers 23 are formed by ridges 24 extending into the lumen of nerve cuff 30. The chambers 23 serve to increase the selectivity of electrical stimulation directed to nerve 20 contained within cuff 30. Specifically, using multichannelled, multi-chambered nerve cuff 30, electrical signals provided by each of electrodes 14 are relatively isolated from one another and a signal from one electrode, or a certain set of electrodes, recruits only specific neurons to produce nervous signals (generally those neurons which are near the specific chamber which hosts the electrode providing the signal). In this manner, selective neurons can be recruited to produce nervous signals by providing signals through particular electrodes.

It will be appreciated that an amputee may appreciate different sensations depending upon which neurons are recruited to send a "sensory signal". If a neuron which had innervated the touch sensors on a fingertip is stimulated, for example, the amputee would have the sensation of this touch.

It has been determined by the present inventor that a plurality of signals may be generated by signal generator 12 and sent to electrodes 14, thereby stimulating various portions of nerve 20. The effect of this, when applied to amputees, is that phantom pain may be alleviated, since the provision of a regular flow of sensory information to the cerebral cortex, and the restoration of a balance of activity in large and small diameter

sensory nerve fibers will tend to inhibit the exaggerated transmission of pain sensations to the sensory brain areas of the amputee.

It has also been discovered that certain patterns of stimulation, generally person-specific, will be more effective than others at alleviating phantom limb pain. In particular, patterns of signals approximating the train of signals received from a normal, innervated limb are have been discovered to be particularly effective. In a preferred embodiment of the present invention, the system may be programmed to optimize such stimulation patterns, or the choice of stimulation patterns may be controlled by the amputee. The amputee may adjust the amplitude and frequency of signals, for example, and also may select which channel (ie. electrode) transmits which signal.

In one method, the voltage, current and charge density per stimulation impulse is preferably in the range of 10-1000 μs in duration, preferably negative going if monophasic, preferably negative/positive if biphasic, and with current amplitude preferably in the range of 1-10 times the threshold current value for first recruitment of large-diameter sensory fibers, in order to not recruit pain fibers of smaller diameter and higher threshold. Threshold can be determined by the lowest level of stimulation that is detected by the amputee as causing a sensation of cutaneous or proprioceptive modality. Another way to determine the maximum stimulation to be used is by having the amputee report the highest level of stimulation that does not cause a noxious or painful sensation and keeping the stimulation safely below the threshold level for pain.

Further, the preferred method may provide the stimulation in trains in the range up to the maximum frequency that is perceived as non-fused tetani by the amputee, which could be as low as 10-20 Hz or as high as 300 Hz (300 impulses per second). The stimulation can be provided as a constant-frequency train, as regular bursts of constant frequency stimuli, as random bursts, as bursts of gradually increasing/decreasing frequency, or in many other patterns that are determined in part by the reported sensations elicited in the amputee and by the expressed preference of the amputee.

Again, while the electrical stimulation system of the present invention can be placed anywhere as long as the signals generated can be effectively transmitted to electrodes 14, in a preferred embodiment of the present invention, it is convenient to incorporate signal generator 12 within a prosthetic limb 40, as shown in Figure 1. Prosthetic limb 40 may also be provided with a plurality of sensors 50 (the 3 sensors shown in Figure 1 are labeled 50A, 50B and 50C), and various motors 60.

As described above, it has been found that the signals sent to nerve 20 to alleviate phantom limb pain are effective when they generally approximate the pattern and train of signals typically seen by the cortex as arising from a normal, innervated limb. It is accordingly desirable to provide a stream of signals to nerve 20 which approximates the normal stream. This can be effectively accomplished by "passing through" signals produced by sensors in the prosthetic limb 40 to nerve 20. Thus, the generator 12 can provide patterns of electrical stimulation to nerve 20 that

depend upon, and approximate, the flow of information to generator 12 from sensors 50 in the prosthetic limb.

In a preferred embodiment, this may be accomplished by providing a microprocessor in conjunction with signal generator 12 which is programmed to accept signals produced by sensors 50, transducing them to be electrical signals sent to nerve 30 by signal generator 12. The sensory signals from sensors 50 may be telemetered directly from a transmitter in the prosthetic limb to a receiver (not shown) implanted in the stump, or the transduction may take place in a transducer and transmitter contained in the prostheses. When the prosthetic limb 40 is in use, the sensory feedback system overrides and substitutes for the background activity from the phantom limb pain treatment stimulator described above, which would be switched on at other times (for example, when the amputee was asleep).

It will be appreciated that the sensory feedback system would operate most effectively if the signals sent to nerve 30 gave the "appropriate" sensation to the amputee upon the activation of a certain sensor in the prosthetic limb 40. For example, it is much preferred that an amputee get the sensation of a fingertip touching something if the touch sensor on a fingertip of the prosthetic limb 40 is stimulated, than some other sensation, although the cortex will over time adapt at least partially to "inaccurate" sensations. The microprocessor can be programmed to send the appropriate signal to an appropriate electrode 14 depending upon the particular signal received from a sensor 50. This will simply require

feedback from the amputee about what sensations are felt upon stimulation of different portions of nerve 30 (ie. different electrodes), and the appropriate matches programmed into the microprocessor.

In a further embodiment of the invention, if the system is equipped with a microprocessor, it may be programmed to monitor various voluntary command signals generated by the amputee together with the sensory information flow arriving from sensors 50 in the prosthetic limb 40 and may thus control the action of the motors 60 placed in the prosthetic limb 40 that control the position and movement of the prosthetic limb joints and digits.

In operation, where the goal is to provide sensory feedback - arising from the prosthetic limb, stimulation preferably will be applied continuously during those periods when the prosthetic limb 40 is connected and in use. When not in use, stimulation may still be applied by signal generator 12 to provide cortical stimulation to keep pain sensation from being interpreted by amputee.

The stimulation will preferably be linked to the intensity of a given sensory input that is being monitored by sensors in the prosthetic limb. For example, for one channel of feedback the monitored input could be grip force, or pressure between the thumb and forefinger. In such case, the intensity of stimulation of the nerve would be graded, within the available dynamic range, to the range of intensities to be monitored. For example if grip force in the range 0-10 N is to be monitored and the

dynamic range of stimulation frequencies detected by the amputee is 0-20 Hz, then the stimulation could be scaled so that every 1 Hz increment represents an increase of 0.5 N and the stimulation frequency range 0-20 Hz represents the grip force range 0-10 N.

For multi-channel systems, essentially similar patterns may be employed, but these can be provided independently to each channel, in such a way that all the stimulation parameters may be different and independently controlled for each channel, and each channel can be dedicated to represent a different sensory modality. For example, if four sensory channels are available for feedback from a hand prosthesis, these can be assigned to represent grip force in the thumb, slip detection in the thumb, angle of the wrist joint, and heat sensed in the palm of the hand. Each of the four sensory inputs would be provided by appropriate sensors built into the prosthetic hand and wrist and would be coded independently as described above for single-channel feedback systems.

It is believed that the systems of the present invention should be implanted as soon as possible following limb amputation (or even before) to provide the greatest benefit, so as to maximally arrest cortical changes subsequent to amputation.

As will be apparent to those skilled in the art in the light of the foregoing disclosure, many alterations and modifications are possible in the practice of this invention without departing from the spirit or scope thereof. For example, it is not critical to the invention to have the electrical

signals produced by a signal generator be transmitted to nerve 20 electrically. The nerve cuff 30 may support the mechanical anchoring of one or more signal transducers, their associated conductors and associated signal processing units. For example, it may be appropriate to have an electrochemical, pharmacological and/or optical system to transduce signals from the signal generator 12 to recruit neurons in nerve 30. Such a pharmacological system 60 is also shown in Figure 1.

Further, while the system described herein is described with particular application to amputees, it may also suitably be employed with appropriate modification to work in subjects with other peripheral nerve injuries other than those caused by amputation.

Accordingly, the scope of the invention is to be construed in accordance with the substance defined by the following claims.

WHAT IS CLAIMED IS:

1. A system for alleviating phantom limb pain in an amputee having a limb stump, said system comprising:

a) a plurality of electrodes implanted in said limb stump, said electrodes placed in close proximity to a severed sensory nerve in the amputee's limb stump, said electrodes when supplied with electrical current providing electrical stimulation to said nerve; and

b) an electrical signal generator fashioned to communicate varying electrical signals to each electrode.

2. The system as claimed in claim 1 wherein said electrodes are incorporated within a tubular nerve cuff fashioned to be implanted in said limb stump so as to circumferentially surround a portion of said nerve.

3. The system as claimed in claim 2 wherein said nerve cuff is multi-chambered, and wherein each of said electrodes is segregated into one chamber of said nerve cuff, each electrode thereby being placed in close proximity to a different portion of said nerve.

4. The system as claimed in claim 3 wherein said electrical signal generator is outside of the amputee's body.

5. The system as claimed in claim 4 wherein said signals generated by said signal generator are communicated by said generator to said electrodes non-electrically, at least in part.

6. The system as claimed in claim 5 wherein said signals generated by said signal generator are communicated telemetrically across the skin of the amputee.

7. The system as claimed in claim 6 wherein said signal generator is contained within a prosthetic limb fashioned to replace the amputee's amputated limb.

8. The system as claimed in claim 7 wherein said prosthetic limb further comprises a plurality of sensors, each of which provides a sensor signal to said signal generator.

9. The system as claimed in claim 8 wherein said signals produced by said generator are responsive to signals produced by said sensors.

10. The system as claimed in claim 9 wherein a plurality of unique electrical signals are communicated to said electrodes, providing stimulation to said nerve approximating the pattern of stimulation arising from an unamputated, normally innervated limb.

11. A method for alleviating phantom limb pain in an amputee, comprising the steps of:

a) equipping an amputee with the system claimed in any one of claims 1-10; and

b) providing a stream of nerve stimulation signals to alleviate phantom limb pain, thereby providing a flow of sensory traffic to the cortex.

12. A system for providing sensory feedback from a prosthetic limb to an amputee having a limb stump, said system comprising:

a) a prosthetic limb having a plurality of sensors, each sensor capable of sensing states of touch, or pressure, or force, or slip, or joint position or temperature, each of said sensors producing a unique sensor signal indicative of a sensed state;

b) a signal transducer contained within said prosthetic limb for transducing each of said unique sensor signals into a unique electrical signal suitable for stimulating action potential activity in nerve fibers;

c) a multi-chambered nerve cuff implanted in said limb stump, said cuff surrounding a severed sensory nerve in said limb stump and incorporating a plurality of electrodes, each of said electrodes when supplied with electrical current providing electrical stimulation to a portion of said nerve; and

d) means for communicating each of said unique electrical signals to a predetermined electrode in said nerve cuff.

13. The system as claimed in claim 12 wherein said means for communicating said unique electrical signals comprises electrical and non-electrically signal transmission in combination.

14. The system as claimed in claim 13 wherein said non-electrically signal transmission comprises telemetric transmission across the skin of the amputee.

15. The system as claimed in claim 14 wherein a plurality of unique electrical signals are communicated to said electrodes, providing stimulation to said nerve approximating the pattern of stimulation arising from an unamputated, normally innervated limb.

16. The system as claimed in claim 15 wherein said predetermined electrode, when sent its signal, stimulates that portion of said nerve which provides to the amputee an appropriate sensation.

17. The system as claimed in claim 10 comprising a plurality of nerve cuffs, each one surrounding a different nerve.

18. A method for providing an amputee with sensory feedback from a prosthetic limb, comprising the steps of:

a) equipping an amputee with the system claimed in any one of claims 12-17; and

b) providing sensory stimuli to said prosthetic limb.

19. A system for alleviating pain in a person having a peripheral nerve injury, said system comprising:

a) a plurality of electrodes implanted in said person, said electrodes placed in close proximity to an injured sensory nerve in said person,

said electrodes when supplied with electrical current providing electrical stimulation to said nerve intermediate the site of injury of said nerve and the cortex; and

b) an electrical signal generator fashioned to communicate varying electrical signals to each electrode.

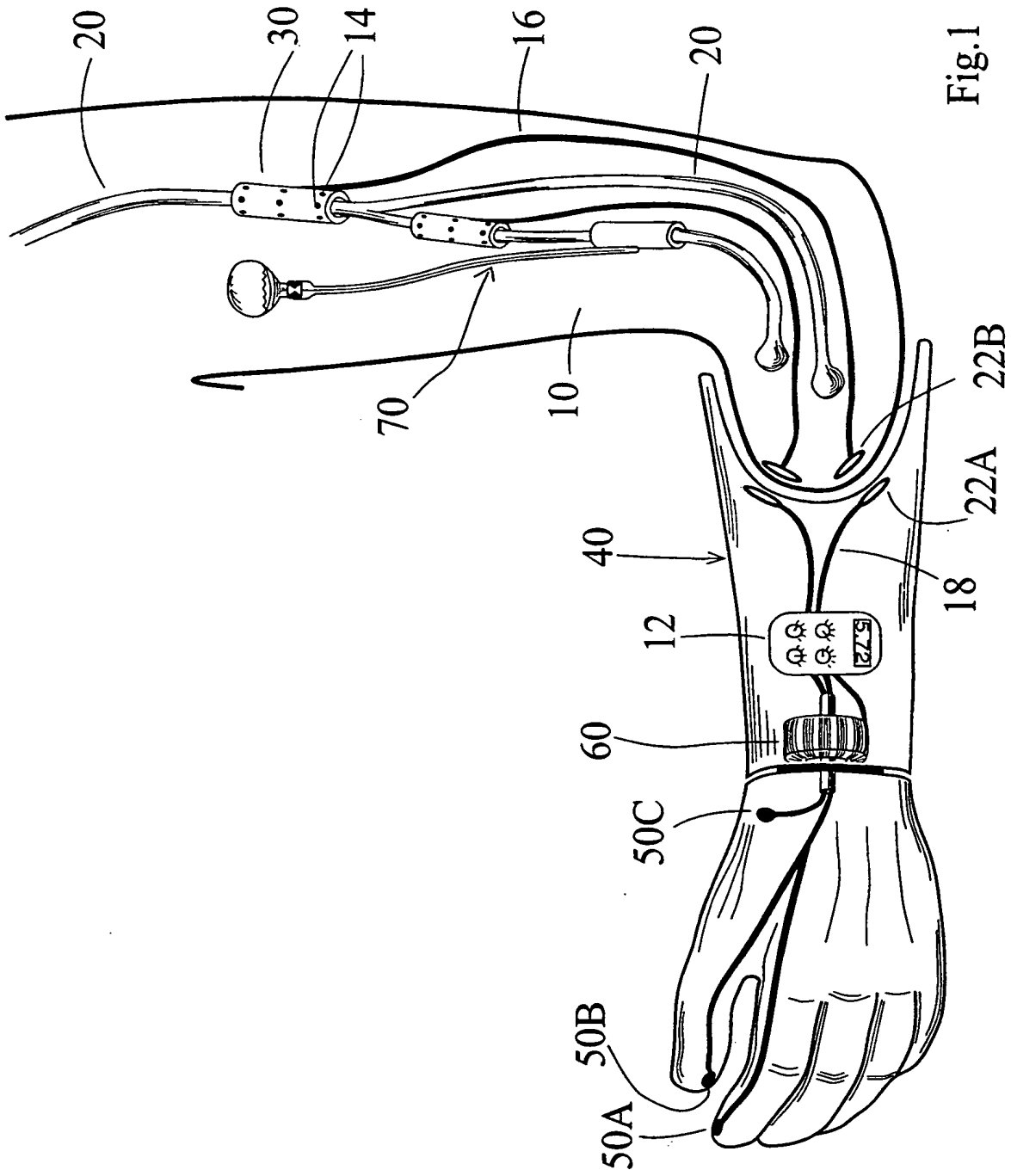

Fig.1

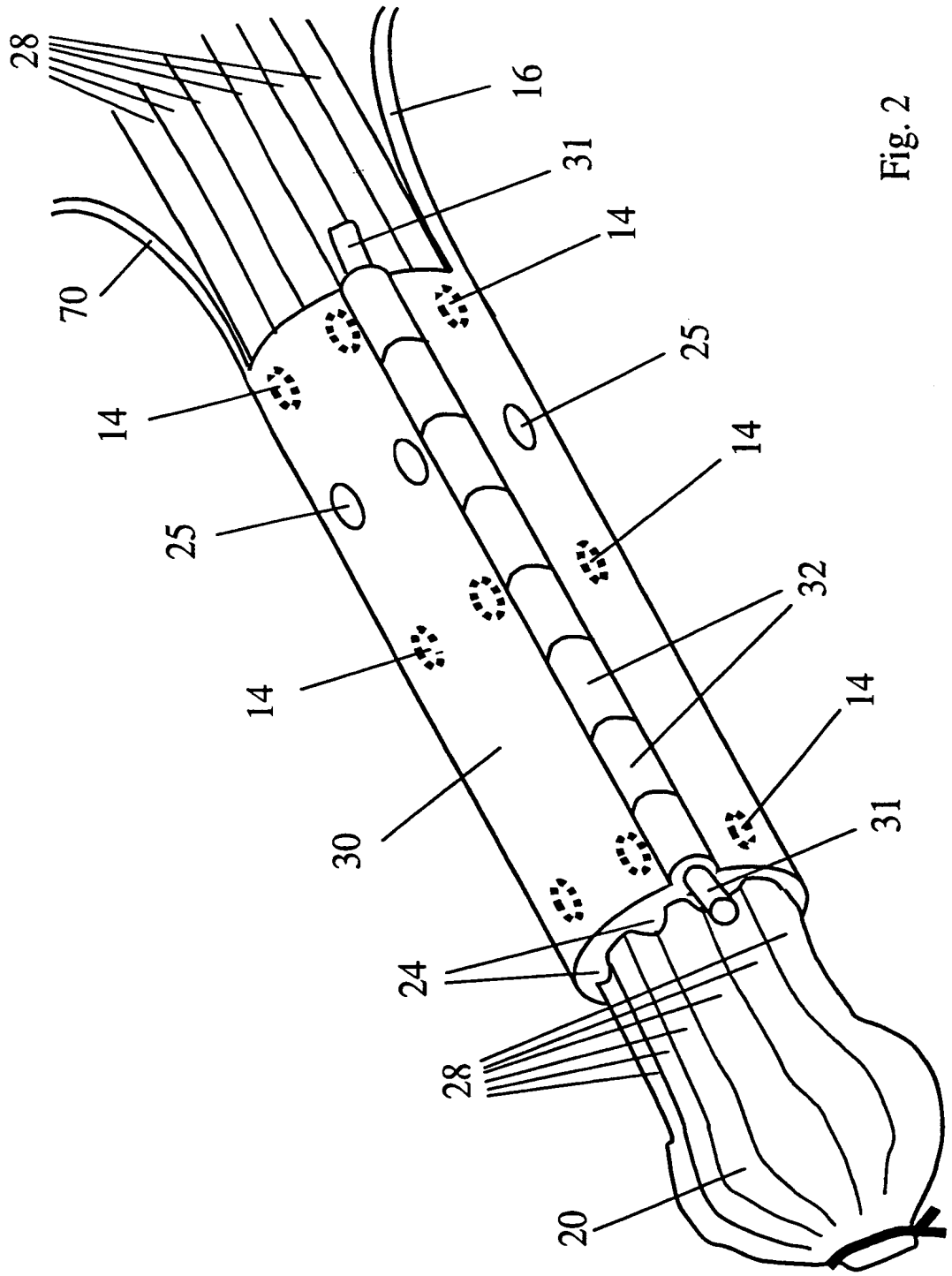

Fig. 2

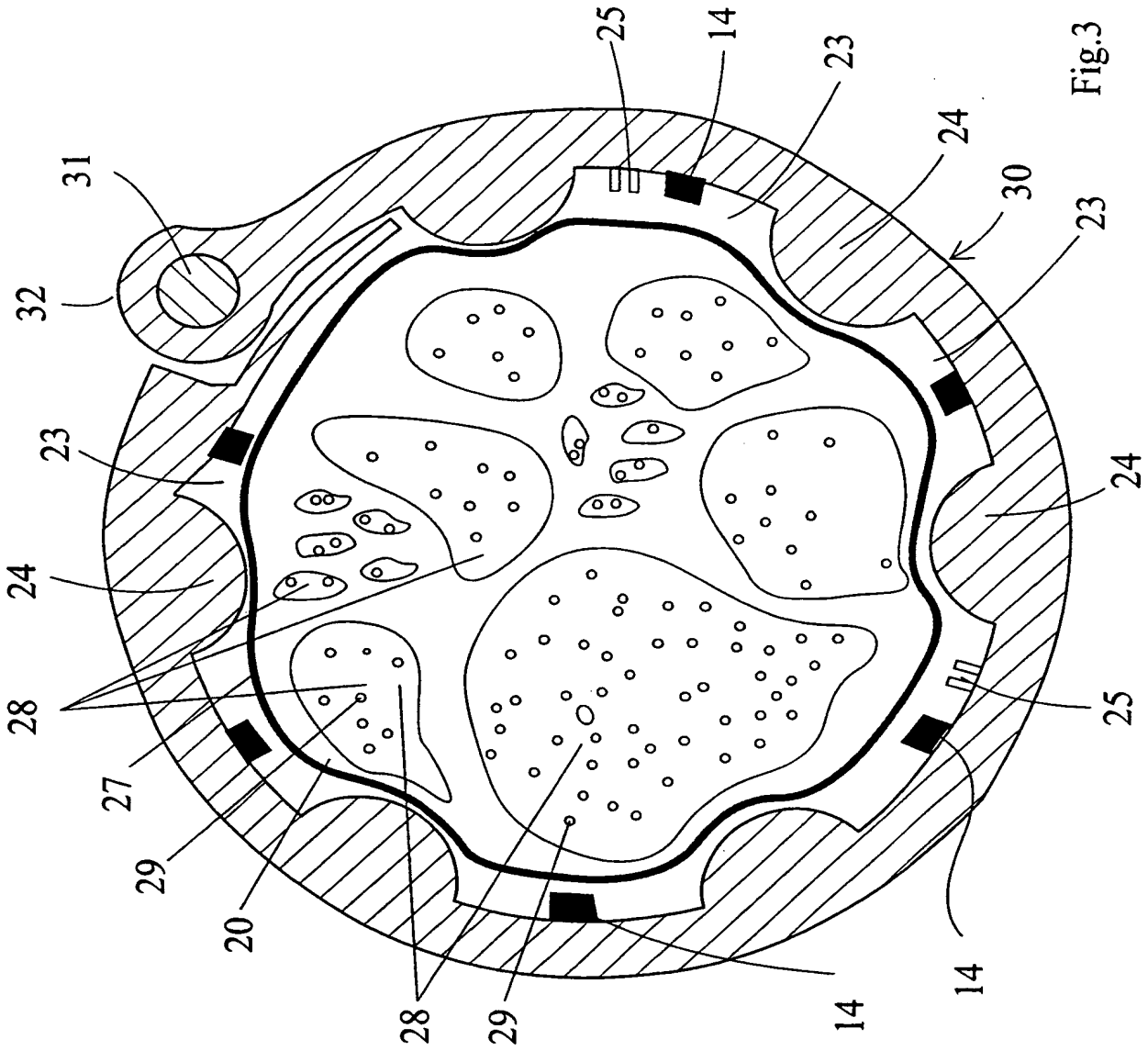

Fig.3